REMARKS

I. Status Of The Claims.

Claims 1, 2, 4-13, 15, 18, 20-25, 27, 29, and 32-34 are pending in the Application. This Response and Amendment amends Claims 1, 11, 12, 20, 27, and 29 and adds new claim 37.

II. Claim Amendments And New Claims.

The claim amendments and new claims are described below. Applicants respectfully submit that these claim amendments and new claims do not add new matter. Entry of the claim amendments and new claims is respectfully requested.

A. Claims 1, 12, 20, 27, and 29.

Claims 1, 12, 20, 27 and 29 have been amended to: (1) substitute "consisting essentially" in place of "comprised;" (2) restore the previously deleted antecedent basis for "the activated support;" and (3) to add that the covalently attached biological molecule is available for use in an assay. Accordingly, these amendments do not add new matter.

B. Claim 11.

Claim 11 is amended replace step "(b)" with step "(d)", which restores the claim's proper dependent form. Accordingly, this amendment does not add new matter.

C. Claim 37

New claim 37 is added to provide an independent claim for a particularly preferred embodiment of the invention, wherein 1,2,4-carbonyl di-triazole is used as an activating compound. Support for the new claim can be found throughout the specification, as well as pending claims 4 and 15. Accordingly, this new claim does not add new matter.

III. The Claimed Invention.

The invention is directed to a method for attaching biological molecules to a solid support in a two-step process. The present invention solves the problems of the prior art, which generally requires more than two steps, by requiring the combination of a solid support with an available amino group, and an activating group, which attaches both the solid support and the biological molecule. The advantages of the claimed invention over the prior art are that it is more efficient, economical, simpler and faster, with greater sensitivity.

For example, the present invention solves problems of the prior art, the acyl fluoride ("AcF") method of attachment disclosed in Milton, U.S. No. 6,143,833 by reducing the number of steps necessary to covalently attach a biological molecule to a solid support, and increasing the loading of biological molecules onto the solid support for synthesis and analyte detection. (*See, e.g.*, Specification, page 1).

IV. The 35 USC § 102 Rejection.

The Office has rejected Claims 1, 2, 9, 12, 13, 18, 29 and 32 under 35 U.S.C. § 102(b) as being anticipated by Jennison et al., (Jennison et al., "Biocoating of Implants with Mediator Molecules: Surface Enhancement of Metals by Treatment with Chromosulfuric Acid: Mat.-wiss. U. Werkstofftech. 1999, 30, 838-845) for the reasons stated in numbered paragraph 6 of the Office Action.

Step (a) of independent Claims 1, 12 and 29 is limited to "providing a solid support consisting essentially of an organic polymer having at least one available amino group". Jennison et al. do not disclose a solid support as set forth in Claims 1, 12 and 29. Accordingly, Applicants request withdrawal of the Rejection under 35 U.S.C. § 102(b) on this basis.

V. The 35 USC § 103 Rejections.

A. The Invention Is Non-Obvious Over Jennison et al. and Stolowitz.

Claims 1,2, 4, 9-13, 15, 18, 29 and 32 are rejected under 35 U.S.C. § 103(a) as unpatentable over Jennison et al., (Jennison et al., "Biocoating of Implants with Mediator Molecules: Surface Enhancement of Metals by Treatment with Chromosulfuric Acid: Mat.-wiss. U. Werkstofftech. 1999, 30, 838-845) and Stolowitz et al. (WO 87/06586) for the reasons stated in numbered paragraph 9 of the Office Action.

Applicants respectfully traverse these rejections on the basis that (1) Jennison et al. is not analogous art; and (2) the Office has not established a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the rejection and allowance of all pending claims on the following basis.

1. Jennison et al. is not analogous art.

> In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicants endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Applicant's invention is directed to the covalent linkage of biological molecules to solid supports for use in diagnostic and analytical procedures, such as assays. In contrast, Jennison et al. is directed to coating bone implantable metals, such as titanium, with biologically active molecules, such as morphogens or growth factors. (See, p. 832, Introduction; see also p. 841 Results & Discussion, first paragraph). Jennison et al.'s method of preparing metal implant surfaces, designed for "controlled release" of biologically active molecules to attract target cells, is not reasonably pertinent to Applicants' problem of assay sensitivity. Indeed, controlled release of biological materials from a metal implant has nothing to do with an assay. Consequently, one of skill in the art of developing diagnostic and analytical procedures would not look to the art of metal implants to solve a problem with retaining biological molecules on polymeric supports to improve assay sensitivity. Since Jennison et al. is non-analogous art, the reference provides no basis for rejecting Applicants's claims under 35 USC 103 (a).

2. The Office Has Not Established a Prima Facie Case of Obviousness over Jennison et al. in view of Stolowitz

Assuming *arguendo*, that Jennison et al, is analogous art, the Office has not established the basic criteria for establishing a *prima facie* case of obviousnes. First, the office has not established the necessary suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of Jennison et al. with Stolowitz. Moreover, the combination of Jennison et al. and Stolowitz do not teach or suggest all the claim limitations.

a. There is no Suggestion or Motivation to Combine Jennison et al. with Stolowitz.

Applicants respectfully submit that the Office has not provided the required suggestion or motivation to combine the references and request withdrawal of the rejection on this basis.

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

As stated above, the Jennison et al. reference, as a whole, is directed to coating bone implantable metals, such as titanium, with biologically active molecules, such as morphogens or growth factors. As stated by the Office, the invention of Stolowitz "relates to the functionalization of particulate bonded phase chromatographic supports prepared by silanization of silica gel or controlled pore glass." The field of endeavor of Jennison et al. (biocompatible implants) is so far removed from that of Stolowitz (chromatographic supports) that the references are non-analogous art with respect to each other.

No where in the Office Action does the Examiner provide a suggestion or motivation to combine a method of making biocompatible titanium implants, as disclosed in Jennison et al. with a method of making chromatographic support materials, as described in Stolowitz. Indeed, substitution of a brittle material like glass or silica for titanium would defeat the purpose of Jennison et al. Likewise, substitution of the "functionalizing reagents" taught by Stolowitz for the biologically active proteins of Jennison would probably diminish the biocompatibility of the implant.

Moreover, Jennison et al. teach the desirability of non-covalent adsorption or chemical bonds which spontaneously hydrolyze to provide a "controlled release" mechanism for biological molecules immobilized on metal implant surfaces. (see Results and Discussion, page 841). Such a "controlled release" mechanism would be anathema to Stolowitz who teaches non-specific interactions are problematic for chromatographic applications. (see, e.g., page 2 paragraph 1).

> Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991)

Stolowitz attempts to eliminate adsorption problems associated with particulate silica or controlled pore glass substrates by preparing a hydrophobic barrier, i.e., a urea linkage, masking the silane backbone and residual silanol activity beneath it (see, e.g., page 4, lines 1-16; page 5 paragraph 1; and page 7, lines 7-13). Twelve years later, Jennison et al. systematically document the irreversible adsorption of ubiquitin and bone morphogenetic protein 2 to Ti-APS-CDI activated supports to arrive at a net value for covalently coupled protein. (See, e.g. page 842, column 1; see, also, Tables 2, 3 and 4). Thus, at the time of Applicants invention, Jennison et al.'s evidence of significant non-specific adsorption of biologically active molecules clearly undermines any suggestion of Stolowitz that his method of introducing urea linkages eliminates the irreversible non-specific adsorption of biological macromolecules on any and all solid supports.

At best, the teachings of Stolowitz' are limited to the activation of silanized silica gel or controlled pore glass chromatographic supports and covalent attachment of several "functionalizing reagents." [1] Moreover, relying on the statement of Stolowitz that "almost [an]

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[1] For example, Stolowitz discloses:

(page 10, paragraph 1) A variety of azolides other than N, N'-carbonyl-diimidazole may be employed in preparation of the activated support, Formula III," wherein Formula III (page 6 lines 8-25) refers to "a bonded phase chromatographic support" prepared "with activated particulate silica or controlled pore glass." (emphasis added);

(Summary of Invention) In addition, a number of specific objectives are also achieved, including: ...The preparation of a urea derivative of a bonded phase chromatographic support and the unique hydrophilic nature of the urea linkage; (emphasis added, see also page 3, lines 14-20 above and page 6, lines 8-25 below);

Example I, which details the covalent linkage of aminopropyl silica gel to glycine;

(Page 3, lines 14-20) The invention relates to the functionalization of particulate bonded phase chromatographic supports prepared by silanization of silica gel or controlled pore glass ... (emphasis added); and

(Page 3, lines 21-26) ... Derivatization results from a reaction of the activated support with a functionalizing reagent consisting of a primary or secondary, alkyl or aryl amine ... A urea linkage results through which the functionalizing reagent is covalently attached to the support. (emphasis added).

infinite variety of ligands … can be employed as functionalizing reagents" (page 4, lines 34-35) epitomizes an "obvious to try" rationale, where "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... " In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Accordingly, one of skill in the art would not look to Stolowitz to teach the deficient limitations of Jennison et al. or be motivated to broadly construe the teachings of Stolowitz to any or all activated supports and functionalizing reagents.

b. The combination of Jennison et al. and Stolowitz do not teach or suggest all the claim limitations

The silanized solid supports of Jennison et al. and Stolowitz consist essentially of inorganic materials, i.e. metal and silica, respectively. Accordingly, neither reference teach or suggest providing a solid support consisting essentially of an organic polymer having at least one available amino group as claimed by Applicants. Indeed, any teaching or suggestion by Stolowitz to introduce a urea linkage is clearly limited to solving the problem of non-specific adsorption by masking the silane backbone and residual silanol activity, i.e. the inorganic silicon based constituents, of silanized silica or controlled pore glass supports.

Moreover, neither reference teaches or suggests covalently attaching a biological molecule to the solid support so that the biological molecule is available for use in an assay as claimed by Applicants. Instead, Jennison et al.'s method provides metal supports, wherein a substantial fraction of the immobilized biological molecules are inherently adsorbed to and/or released from the surface in a manner unsuitable for use in an assay. Stolowitz provides no teaching or suggestion of covalently attaching any biological molecules in accordance with Applicants' claim limitations. Accordingly, the Office has not established a *prima facie* case for the combination of Jennison et al. with Stolowitz.

B. The Invention Is Non-Obvious Over Jennison, Stolowitz, Milton, Okamoto, and Guo.

Claims 1,2,-13,15,18,20-25,27,29 and 32-34 are rejected under 35 U.S.C. § 103(a) as unpatentable over Jennison et al., (Jennison et al., "Biocoating of Implants with Mediator Molecules: Surface Enhancement of Metals by Treatment with Chromosulfuric Acid: Mat.-wiss. U. Werkstofftech. 1999, 30, 838-845) and Stolowitz et al. (WO 87/06586) and Milton (US 6,146,833) and Okamoto et al. (US 6,476,215) and Guo et al. (Nuc. Acids Res. 1994, pp. 5456-5465) for the reasons stated in numbered paragraph 9 of the Office Action.

Applicants respectfully traverse these rejections on the basis that (1) Jennison et al. is not analogous art; (2) the Office has not established a *prima facie* case of obviousness; (3) the references teach away from the claimed method; and (4) any such *prima facie* case is rebutted by the evidence of the superior and unexpected results of Applicants' claimed method for attaching a biological molecule. Applicants respectfully request withdrawal of the rejection and allowance of all pending claims on the following basis.

1. Jennison et al. is not analogous art.

As detailed above, the field of endeavor of Jennison et al. (medical implants) is remote from the field of Applicants' claimed invention (diagnostic and analytical procedures, such as assays). Moreover, Jennison et al.'s method of preparing metal implant surfaces, designed for "controlled release" of biologically active molecules to attract target cells, is not reasonably pertinent to Applicants' problem of diminished assay sensitivity, due to low retention of biological molecules on polymeric supports. Since Jennison et al. is non-analogous art, the reference provides no basis for rejecting Applicants's claims under 35 USC 103 (a).

2. The Office Has Not Established A Prima Facie Case Of Obviousness Further Over Milton, Okamoto, and Guo For Claims 5-8, 20-25, 27, 33 and 34.

Claims 1, 2, 4, 9-13, 15, 18, 29 and 32 are non-obvious over Jennison and Stolowitz for the reasons stated in paragraphs VI(A)(1-2) above. Neither Jennison nor Stolowitz teach the limitations of claims 5-8, 20-25, 27, 33 and 34. Consequently, the Office looks to Milton et al.,

Okamoto et al., and Guo et al. to remedy the deficiencies of Jennison and Stolowitz. (Office Action, pages 9-12).

Applicants respectfully submit that the Office has not further established a *prima facie* case of obviousness with respect to Claims 5-8, 20-25, 27, 33 and 34 and requests withdrawal of the rejection on this basis.

a. There is no Suggestion or Motivation to Combine Jennison et al. and Stolowitz with Milton, Okamoto and Guo.

The Office has not provided a motivation to combine Jennison, and Stolowitz with Milton, Okamoto et al., and Guo et al. as required to establish a *prima facie* case of obviousness with regard to Claims 5-6 and 22-23. See, Office Action page 14, lines 4-14. Further, Applicants submit that the references themselves to not provide the requisite motivation to modify or combine the references to arrive at Applicants invention.

Initially, Applicants would like to point out that any suggestion, as set forth on page 14, lines 4-14 of the Office Action, to:

> immobilize affinity ligands in an array format for analytical and diagnostic purposes… using the CDI immobilization procedures taught by Jennisson et al. and Stolowitz et al. because Stolowitiz et al., for example, explicitly state that CDI can be used for this purpose…

is factually incorrect. Applicants were unable to locate any teaching or suggestion corresponding to column 6, lines 43-56 or lines 23-46, within the Stolowitz reference, as set forth in the Office Action. The Stolowitz reference has no columns, only page numbers. Moreover, the Jennison and Stolowitz references, as a whole, are silent regarding the use of CDI immobilization techniques for diagnostic purposes. Accordingly, the Office has not provided the requisite motivation to modify the CDI immobilization techniques of Jennison et al. and Stolowitz et al. to provide affinity ligands for use as diagnostic reagents, e.g., on the inner surface of a microtitre plate.

Nor has the Office provided a motivation to combine Jennison and Stolowitz with Milton, Okamoto and Guo as required to establish a *prima facie* case of obviousness with regard to Claims 20, 27 and 33. See, Office Action page 12, line 21, through page 13, line 4. Nowhere in the Office Action does the Examiner provide a suggestion or motivation to combine the derivatized polypropylene films of Milton with the activating compounds disclosed in Jennison or Stolowitz. Instead, the Office merely asserts the disclosure of "aminated polypropylene" by Milton. Further, Applicants submit that the references themselves do not provide the requisite motivation to modify or combine the references to arrive at Applicants invention.

b. The combination of Jennison , Stolowitz, Milton, Okamoto and Guo fail to teach or suggest all the claim limitations

None of the cited references teach or suggest forming an "activated support" as claimed by applicants. Milton, Guo and Okamoto fail to cure the deficiencies of Jennison and Stolowitz, Guo with respect to claims 1-13, 15, 18, 29 and 32-34 as none of the cited references teach or suggest reacting "a solid support consisting essentially of an organic polymer having at least available amino group" with an activating compound as claimed by applicants "so that the reaction results in L_1 being displaced by the available amino group on the solid support to form an activated support"

For example, Milton teaches immobilizing biopolymers on solid supports having acyl fluoride functionalities. As described throughout Milton, and shown in the scheme in Cols. 17-19 of Milton, aminated polypropylene is disclosed, among a myriad of other polymeric materials, as a starting material that is derivatized to have carboxyl functionalities. The carboxyl functionalities are then treated with a suitable reagent for forming an acyl fluoride functionality. Milton's disclosure that "carbodiimides will convert carboxyl groups to an isourea" (see column 8, lines 37-55) merely suggests an alternative treatment of starting materials derivatized to have carboxyl functionalities, not amino groups. Accordingly, the combined teachings of Jennison, Stolowitz, Milton, Guo and Okamoto provide no motivation to react, e.g., CDI, with an available amino group on any of the solid supports selected by Applicants, to form an activated support.

Smilarly, none of the cited references teach or suggest reacting an aminated solid support "formed from a material selected from group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon" with an activating compound applicants "so that the reaction results in L_1 being displaced by the available amino group on the solid support to form an activated support" in accordance with claims 20-25 and 27.

Further, none of the cited references teach or suggest "reacting the biological molecule" with any of Applicants' novel and non-obvious activated supports. For example, the procedure for immobilizing biopolymers disclosed in Milton is a three-step process, *i.e.*, (1) derivatizing the aminated substrate to a carboxylated substrate; (2) treating the carboxylated substrate to form an acyl fluoride functionality; and (3) reacting the acyl fluoride functionality on the substrate with a biopolymer. In contrast, Applicants' claimed method is a two-step process where an activating compound is reacted with both an amino group on a solid support and a biological molecule.

In another example (Ex. 9 of Milton), one step of the multi-step peptide synthesis procedure describes treating a solid support, modified with a linker, with diisopropylcarbodiimide in conjunction with bromoacetic acid. This step is followed by a further reaction with cysteamine and yet another step to attach a glycine to the linker. The glycine residue then provides the starting material for further step by step addition of additional amino acid residues to form a polypeptide chain. Accordingly, Ex. 9 provides no teaching or suggestion that a "biological molecule," in accordance with applicants claims, will react with a diisopropylcarbodiimide activated support, thereby displacing a leaving group (L2) of the activating compound and covalently attaching the biological molecule to the solid support.

Likewise, Milton et al.'s teaching that "any protein or peptide with surface amino groups, e.g., lysine can be immobilized to a solid support having pendant acyl fluoride functionalities (column 4, lines 28-30, emphasis added) does not teach or suggest reacting a biological molecule with, e.g., a CDI activated support.

Applicants request withdrawal of the rejection and allowance of all pending claims as the combination of Jennison , Stolowitz, Milton, Okamoto and Guo fail to teach or suggest all the claim limitations.

3. The Cited References Teach Away from Applicants Invention

As detailed above, Applicants do not admit that the Office has established a *prima facie* case of obviousness. However, even if a *prima facie* case of obviousness has been established, it is rebutted by a teaching away from Applicants' claimed invention.

Applicants request withdrawal of the rejection and allowance of all claims based on the following teachings of Jennison and Milton.

a. Jennison Teaches Away from Applicants Invention

Each of the independent claims is limited to a "a solid support … having at least one available amino group"; "reacting the available amino group on the solid support with an activating compound, the activating compound having the structure: $L_1 - X - L_2$;" and "covalently attaching the biological molecule to the solid support so that the biological molecule is available for use in an assay." These limitations are expressly taught away from in Jennison and under USPTO practice and procedure, the references must be considered in their entirety. MPEP § 2141.02.

Initially Applicants would like to point out that Jennison teaches the general desirability of non-covalent attachment of biomolecules, such as a polypeptide chain, and/or chemical bonds which spontaneously hydrolyze to provide a "controlled release" mechanism for biological molecules immobilized on metal implant surfaces. Moreover, the Jennison reference documents non-specific binding of biological molecules to the solid support, before and after CDI activation of aminoalkyl silanes. Accordingly, Jennison teaches that forming an activated support by reacting an available amino group on a solid support with at least one of Applicants claimed activating compounds, e.g., carbodiimide, is a precursor to subsequent non-specific binding of biological molecules to the solid support. Given the admitted criticality of eliminating such non-specific binding for diagnostic assays (see, e.g., Office Action, page 15, lines 9-14 and Milton, column 6, lines 38-43), Jennison et al. teaches away from selecting CDI immobilization techniques for "covalently attaching the biological molecule to the solid support so that the biological molecule is available for use in an assay."

b. Milton Teaches Away From Applicants Invention.

As detailed above, Applicants do not admit that the Office has established a *prima facie* case of obviousness. However, even if a *prima facie* case of obviousness has been established, it is rebutted by a teaching away from Applicants' claimed invention.

Each of the independent Claims is limited to a "a solid support comprised of an organic polymer having at least one available amino group" and "reacting the available amino group on the solid support with an activating compound, the activating compound having the structure: $L_1 - X - L_2$." These limitations are expressly taught away from in Milton and under USPTO practice and procedure, the references must be considered in their entirety. MPEP § 2141.02. Applicants request withdrawal of the rejection and allowance of all claims based on the following teachings of Milton.

Initially Applicants would like to point out that Milton teaches the general unsuitability of covalent attachment of biomolecules, such as an oligonucleotide, using Applicants claimed activating compounds, such as a carbodiimide For example, col. 1, lines 43-56 states:

> presynthesized or natural oligonucleotides have been immobilized by covalently attaching activated oligonucleotides to the solid support. Typically, this approach requires activating the oligonucleotide with e.g., a carbodiimide. Unfortunately, the activated oligonucleotides are expensive and they have short useful lives because they are very unstable. Thus, preparing and utilizing these activated oligonucleotides often lead[s] to the loss of expensive reagents when the activated oligonucleotide decays to an inactive form.

Next, Milton more particularly teaches the unsuitability of carbodiimide activation in the presence of organic solvents (see, e.g., claim 9).

> Moreover, carbodiimide activation frequently results in urea side product formation. Since these ureas tend to be insoluble in many common organic solvents their presence in automated reaction systems can cause problems when tubing and other lines are clogged by the precipitate.

Milton teaches aminated polymers for use as a starting material only in the context of further derivatizing the aminated polymers to form an acyl fluoride functionality. Indeed, Milton teaches away from otherwise activating aminated polymers by blocking any residual amino

groups on propylene films that are not carboxylated. (Milton, column 17 line 9 to column 18 line 4).

Milton further teaches away from the combination of aminated polymers with Applicants claimed activating compound, in view of Jennison et al. The Jennison reference documents non-specific binding of biological molecules to the solid support, before and after CDI activation of aminoalkyl silanes. However, Milton states that: "This [non-specific binding] is an important consideration because diagnostic applications which depend upon detecting reagents specifically bound to biopolymers immobilized to solid supports cannot tolerate non-specific binding to the solid support." (Milton, col. 6, lines 38-43). It is improper to combine references where the references teach away from their combination. MPEP § 2145(X)(D)(2).

Accordingly, one of skill in the art, considering Milton in its entirety, would not be motivated to select an aminated polypropylene, and combine it with an activating compound, such as those cited by the Examiner in Jennison and Stolowitz, as Milton describes numerous problems associated with such a covalent attachment. These problems include the instability of CDI activated compounds, the formation of insoluble urea side products and the likelihood of non-specific binding of biological molecules to the solid support. Applicants request that the Office consider all the teachings of Milton, withdraw the rejection and allow all pending claims, Claims 1-15, 18, 20-25, 27, 29, and 32-34.

4. Applicant's Invention Exhibits Significant And Unexpected Results Over The Prior Art.

Applicants submit that, insofar as the claims may be *prima facie* obvious (which is denied), any such *prima facie* case is rebutted by the evidence of the superior and unexpected results of Applicants' claimed method using 1,2,4-carbonyl di-triazole, as set forth in claims 4, 15 and 37, for attaching a biological molecule.

It is well-settled law that a prima facie case of obviousness under 35 U.S.C. § 103 can be rebutted by evidence that the claimed invention provides unexpected advantages, and that evidence provided by the specification itself must be considered. The experimental results set out in the specification provide evidence that the claimed invention provides unexpected advantages for attaching a biological molecule. In particular, the test results summarized in

Examples 2 and 3 of the Specification are evidence of the remarkable ability of the claimed invention to attach a biological molecule, exhibiting increased oligonucleotide loading and higher sensitivity for analyte detection than the prior art acyl fluoride (AcF) method, an example of the method disclosed in Milton, and a CDI method, as taught by Hermanson et al.

Applicants submit that insofar as it may be *prima facie* obvious to modify or combine Jennison , Stolowitz, Milton, Okamoto and Guo, the use 1,2,4-carbonyl di-triazole as set forth in claims 4, 15 and 37, provides unexpected advantages. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 103 and allowance of claims 4, 15 and 37.

CONCLUSION

The Applicant believes that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicants representative.

The Commissioner is authorized to charge the fee of $1,020, the fee for a three-month extension, to Deposit Account No. 19-2090. The Commissioner is further authorized to charge any other fees associated with this Response and Amendment to Deposit Account No. 19-2090.

Respectfully Submitted,
SHELDON & MAK PC

Date: June 29, 2006

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